

Dynamic Analysis of Bet-Hedging Strategies as a Protection Mechanism against Environmental Fluctuations

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Abstract—In order to increase their robustness against environmental fluctuations, many biological populations have developed *bet-hedging* mechanisms in which the population ‘bets’ against the presence of prolonged favorable environmental conditions by having a few individual behaving as if they sensed a threatening or stressful environment. As a result, the population (as a whole) increases its chances of surviving environmental fluctuations in the long term, while sacrificing short-term performance. In this paper, we propose a theoretical framework, based on Markov jump linear systems, to model and evaluate the performance of bet-hedging strategies in the presence of stochastic fluctuations. We illustrate our results using numerical simulations.

I. INTRODUCTION

Biological populations, such as bacterial colonies, are subject to multiple sources of environmental fluctuations, from regular cycles of daily light and temperature to irregular fluctuations of nutrients and pH levels [1]–[3]. In order to increase their robustness against environmental fluctuations, many biological systems have developed *bet-hedging* mechanisms [3], [4] in which the population ‘bets’ against the presence of prolonged favorable environmental conditions by having a few individual behaving as if they sensed a threatening or stressful environment. For example, in bacterial colonies, some bacteria may stochastically switch into a state of slow metabolic state, in which they are more robust against pH fluctuations. As a result, the population (as a whole) increases its chances of surviving pH fluctuations in the long term, while sacrificing short-term performance. Similar bet-hedging strategies can be found in many other biological systems, such as the lysis-lysogeny switch of bacteriophage λ [5], delayed germination in plants [6], and phenotypic variations in bacteria [7].

In this paper, we pay special attention to a particular type of bet-hedging mechanism based on introducing delays in the function of a few individuals in the population. For example, in the case of cell populations, the presence of time-delays in some basic patterns of cell proliferation can significantly improve the overall population fitness [8]. Similarly, delayed germination in plant populations [6] and delayed disease activation of viruses [9] have also been reported as bet-hedging strategies in biological systems.

In the current literature, the performance of bet-hedging strategies is evaluated using either extensive numerical simulations, or overly simplistic assumptions. Based on numerical simulations, the authors in [10] found the optimal rates of adaptation (e.g., the rate at which bacteria switch into a slow metabolic state) to maximize the growth rate of cell populations. Based on overly simplistic assumptions, analytical calculations of growth rates of phenotypically heterogeneous populations are performed by assuming that environmental fluctuations are either slow enough [1], fast enough [11], or periodic [12]. Although the works mentioned above provide intuitive explanations about the effects of bet-hedging strategies, there is still a lack of a solid mathematical framework for the evaluation of bet-hedging strategies under complex environmental fluctuations.

The aim of this paper is to present a rigorous and tractable framework to quantify the growth rates of cell populations using bet-hedging strategies involving time-delays. Building on the models in the literature [1], [10], [13], we introduce a population model in terms of positive Markov jump linear systems [14] with delays. Among various types of delays, we specifically focus on those in proliferation (i.e., in the state variables) and in adaptation to environmental changes (i.e., in the switching signals). In the former case, we show that the growth rate of a population exhibiting both point and distributed delays is upper-bounded by the maximum real eigenvalue of a particular Metzler matrix. In the latter case, we consider stochastic delays in adaptation to environmental fluctuation and show that the growth rate coincides with the maximum real eigenvalue of a Metzler matrix. The proposed framework can also be used to study both point and distributed delays in the state variables in a unified manner, whereas these delays have been studied separately in the literature [15], [16].

This paper is organized as follows. After presenting the notation in Section II, we introduce several linear growth models of bet-hedging populations involving time delays. Then, in Section III, we derive an upper bound on the growth rates for the case of delayed proliferation. Section IV shifts our focus to delayed adaptation and shows that the growth rate equals the maximum eigenvalue of a Metzler matrix. Numerical simulations are presented in Section V.

A. Mathematical Preliminaries

We denote by \mathbb{R}_+ the set of nonnegative real numbers. The 1-norm of $x \in \mathbb{R}^n$ is defined by $\|x\| = \sum_{i=1}^n |x_i|$. The symbol $\mathbb{1}_n$ denotes the column vector of length n whose entries are all one. By u_i , we denote the i -th canonical

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basis vector in \mathbb{R}^n . Let $U_{ij} = u_i u_j^\top$. We say that a matrix is nonnegative if its entries are nonnegative. A square matrix is said to be *Metzler* if its off-diagonal entries are nonnegative. We say that a matrix is Hurwitz stable if all of its eigenvalues have negative real parts. The Kronecker product [17] of matrices is denoted by \otimes . It is known [17] that, if the standard product of matrices AB and CD are well-defined, then

$$(AB) \otimes (CD) = (A \otimes B)(C \otimes D). \quad (1)$$

For a closed interval $[a, b]$, the space $C([a, b], \mathbb{R}_+^n)$ is defined as the set of \mathbb{R}_+^n -valued continuous functions on $[a, b]$ equipped with the norm $\|x\| = \int_a^b \|x(t)\| dt$.

Let A_0 be an $n \times n$ Metzler matrix, A_1, \dots, A_m be $n \times n$ nonnegative matrices, h_1, \dots, h_m be nonnegative constants, and $B: [0, \infty) \rightarrow \mathbb{R}_+^{n \times n}$ be a continuous function having a compact support. Consider the positive linear system with delay [18]:

$$\frac{dx}{dt} = A_0 x(t) + \sum_{i=1}^m A_i x(t - h_i) + (B * x)(t), \quad (2)$$

where $*$ denotes the convolution. Let T be the minimum number such that $T \geq h_i$ for every $i \in \{1, \dots, m\}$ and the interval $[0, T]$ contains the support of B . We set the initial condition of (2) as $x|_{[-T, 0]} = \phi$ for a function $\phi \in C([-T, 0], \mathbb{R}_+^n)$. We say that the system (2) is *exponentially stable* if there exist $C > 0$ and $\lambda < 0$ such that $\|x(t)\| \leq C e^{\lambda t} \|\phi\|$ for all ϕ and $t \geq 0$. The following stability characterization is given in [18]:

Proposition 1.1 ([18, Theorem III.1]): The system (2) is exponentially stable if and only if the matrix $A_0 + \sum_{i=1}^m A_i + \int_0^\infty B(\tau) d\tau$ is Hurwitz stable.

We also give a review on random variables and stochastic processes. Let (Ω, \mathcal{M}, P) be a probability space. For an integrable random variable X on Ω , its expected value is denoted by $E[X]$. If $\mathcal{M}_1 \subset \mathcal{M}$ is a σ -algebra, then $E[X | \mathcal{M}_1]$ denotes the conditional expectation of X given \mathcal{M}_1 . It is well known (see, e.g., [19]) that

$$E[X] = E[E[X | \mathcal{M}_1]]. \quad (3)$$

Let $f, g: \mathbb{R} \rightarrow \mathbb{R}^n$ be continuous functions having their compact supports in $[0, \infty)$. Let N_1, \dots, N_m denote Poisson counters. We say that a left-continuous function x taking values in \mathbb{R}^n is a solution of the stochastic differential equation

$$dx = (f * x) dt + \sum_{i=1}^m (g_i * x) dN_i \quad (4)$$

if we have $dx/dt = (f * x)(t)$ when no jump occurs at time t , and $x(t^+) = x(t^-) + (g_i * x)(t^-)$ when N_i jumps at time t . For the sake of completeness, we state the Itô rule for stochastic differential equations with Poisson jumps (see, e.g., [20]):

Lemma 1.2: Assume that x follows the stochastic differential equation (4). Let $\psi: \mathbb{R}^n \rightarrow \mathbb{R}^m$ be a differentiable function and define $y(t) = \psi(x(t))$ for every $t \geq 0$. Then, y follows the stochastic differential equation $dy = (d\psi/dx)(f * x) dt + \sum_{i=1}^m (\psi(x + (g_i * x)) - \psi(x)) dN_i$.

II. DELAYED MODELS FOR BET-HEDGING POPULATIONS

The aim of this section is to introduce models of bet-hedging populations involving delays. We first review the delay-free population model given in [1], [10]. Building on this model, we then introduce two models of bet-hedging populations involving delays in their state variable and mode signals, respectively.

Let us consider a biological population growing in an environment fluctuating among n different environment types. The fluctuation is modeled [1] by a time-homogeneous Markov process $\varepsilon = \{\varepsilon(t)\}_{t \geq 0}$ taking values in $\{1, \dots, n\}$ and having the infinitesimal generator $\Pi = [\pi_{ij}]_{i,j \in \mathbb{R}^{n \times n}}$. Therefore, the transition probability of the environment is given by

$$P(\varepsilon(t+h) = j | \varepsilon(t) = i) = \begin{cases} \pi_{ij} h + o(h), & i \neq j, \\ 1 + \pi_{ii} h + o(h), & i = j, \end{cases}$$

where $o(h)/h \rightarrow 0$ as $h \rightarrow 0$. Each individual in the population can exhibit one of n different phenotypes $1, \dots, n$. We assume that the population having phenotype k grows with the instantaneous rate $g_i^k \geq 0$ under environment i . The phenotypes of individuals are assumed to dynamically change, and the rate of switch from phenotype k to phenotype ℓ under environment i is denoted by $\omega_i^{k\ell} \geq 0$. We define $\omega_i^{kk} = -\sum_{\ell \neq k} \omega_i^{k\ell}$. Let $x_k(t)$ denote the number of individuals having phenotype k at time t . Then, the growth of the population can be modeled [1], [10] by the differential equations

$$\Sigma_0: \frac{dx_k}{dt} = g_{\varepsilon(t)}^k x_k(t) + \sum_{\ell=1}^n \omega_{\varepsilon(t)}^{k\ell} x_\ell(t), \quad k = 1, \dots, n.$$

Building on this model, we below introduce two growth models of population involving delays.

A. Delayed Proliferation

We first consider a dynamic model of bet-hedging consisting in introducing delays in state variables of the population. Such delays, which can arise from delayed bet-hedging [9] or delayed proliferation [8], make the derivative dx_k/dt depend not only on the size of the current populations, but also on their past values. To deal with this case, we extend the basic model Σ_0 as follows

$$\Sigma_1: \frac{dx_k}{dt} = g_{\varepsilon(t)}^k x_k(t) + \sum_{\ell=1}^n \omega_{\varepsilon(t)}^{k\ell} x_\ell(t) + p_{\varepsilon(t)}^k x_k(t - d_{\varepsilon(t)}^k) + \int_0^\infty q_{\varepsilon(t)}^k(\tau) x_k(t - \tau) d\tau, \quad k = 1, \dots, n.$$

It is naturally assumed that p_k^i is a nonnegative number and q_k^i is a nonnegative function having a finite support in $[0, \infty)$ for all $k, i \in \{1, \dots, n\}$. We specify the initial condition of the system Σ_1 by

$$x_k|_{[-T, 0]} = \phi_k \in C([-T, 0], \mathbb{R}_+), \quad k = 1, \dots, n,$$

where T is the minimum number such that $d_i^k \leq T$ and $[0, T]$ contains the support of function q_i^k for all $k, i \in \{1, \dots, n\}$.

We define the growth rate of the model Σ_1 as follows:

Definition 2.1: For $\lambda \in \mathbb{R}$, we say that Σ_1 is λ -exponentially stable if there exists $C > 0$ such that $E[\sum_{k=1}^n x_k(t)] \leq Ce^{\lambda t} \sum_{k=1}^n \|\phi_k\|$ for all ϕ_1, \dots, ϕ_n , and $\varepsilon(0) \in \{1, \dots, n\}$. We define the growth rate of Σ_1 as the infimum of λ such that Σ_1 is λ -exponentially stable. If the growth rate of Σ_1 is negative, then we say that Σ_1 is exponentially stable.

B. Delayed Adaptation

Another type of delay in bet-hedging populations can be present in the adaptation of the population to environmental fluctuations. In this case, each individuals' information σ about the environment (on which their adaptation is based on) does not necessarily coincide with the environment ε due to delays. This implies that, mathematically speaking, there exists a nonnegative stochastic process $h = \{h(t)\}_{t \geq 0}$ such that $\sigma(t) = \varepsilon(t - h(t))$. We assume that the growth rates depends on the environmental variable ε , while the adaptation rates between phenotypes depend on the delayed information σ . In this situation, the basic population model Σ_0 has to be rewritten as

$$\Sigma_2 : \frac{dx_k}{dt} = g_{\varepsilon(t)}^k x_k(t) + \sum_{\ell=1}^n \omega_{\sigma(t)}^{\ell k} x_{\ell}(t), \quad k = 1, \dots, n. \quad (5)$$

We postpone the detailed description of the delay process h as well as the definition of the growth rates to Section IV.

III. GROWTH RATE WITH DELAYED PROLIFERATION

The aim of this section is to prove the following theorem, which enables us to find an upper bound of the growth rate of Σ_1 :

Theorem 3.1: Let $\lambda \in \mathbb{R}$ be arbitrary. For all $i, j \in \{1, \dots, n\}$ and $t \geq 0$, define $f_{ij}^{(\lambda)} = p_i^j e^{-\lambda d_i^j} ((U_{ji} e^{\Pi^\top d_i^j}) \otimes u_j^\top)$ and $g_{ij}^{(\lambda)}(t) = q_i^j(t) e^{-\lambda t} ((U_{ji} e^{\Pi^\top t}) \otimes u_j^\top)$. Let

$$\begin{aligned} \bar{A}_{ij}^{(\lambda)} &= u_i \otimes f_{ij}^{(\lambda)}, \\ \bar{B}_{ij}^{(\lambda)}(t) &= u_i \otimes g_{ij}^{(\lambda)}(t). \end{aligned}$$

Then, the growth rate of Σ_1 is less than λ if the matrix

$$\bar{T}^{(\lambda)} = \bar{A}_0 - \lambda I + \sum_{i,j=1}^n \bar{A}_{ij}^{(\lambda)} + \sum_{i,j=1}^n \int_0^\infty \bar{B}_{ij}^{(\lambda)}(t) dt$$

is Hurwitz stable.

Remark 3.2: We can use Theorem 3.1 and a bisection search to find the suboptimal upper bound on the growth rates. We also remark that, when Σ_1 has no delay, the sufficient condition in Theorem 3.1 is also necessary by [14, Theorem 5.1].

The rest of this section is devoted to the proof of Theorem 3.1. We first introduce a vectorial representation of Σ_1 . For each $i \in \{1, \dots, n\}$, define $G_i = \text{diag}(g_i^1, \dots, g_i^n)$, $\Omega_i = [\omega_i^{k\ell}]_{k,\ell}$, $A_i = G_i + \Omega_i^\top$, and $Q_i = \text{diag}(q_i^1, \dots, q_i^n)$. Let

$$x = \begin{bmatrix} x_1 \\ \vdots \\ x_n \end{bmatrix}, \quad (\mathcal{P}_i x)(t) = \begin{bmatrix} p_i^1 x_1(t - d_i^1) \\ \vdots \\ p_i^n x_n(t - d_i^n) \end{bmatrix}, \quad \phi = \begin{bmatrix} \phi_1 \\ \vdots \\ \phi_n \end{bmatrix}.$$

We can then write Σ_1 in a vector form as

$$\Sigma_1 : \frac{dx}{dt} = A_{\varepsilon(t)} x(t) + (\mathcal{P}_{\varepsilon(t)} x)(t) + (Q_{\varepsilon(t)} * x)(t)$$

with initial condition $x|_{[-T,0]} = \phi$. Let us also introduce the vectorial representation $\eta = \{\eta(t)\}_{t \geq 0}$ for the environmental variable ε by $\eta_i(t) = 1$ if $\varepsilon(t) = i$ and $\eta_i(t) = 0$ otherwise. Notice that $\eta(t) = u_{\varepsilon(t)}$.

In what follows, instead of directly dealing with the process $x(t)$, we shall study the auxiliary processes given by [14]

$$z(t) = \eta(t) \otimes x(t), \quad \zeta(t) = E[z(t)], \quad t \geq 0.$$

Notice that neither $z(t)$ nor $\zeta(t)$ is defined when $t < 0$ because $\eta(t)$ is defined only for $t \geq 0$. The next lemma shows that these auxiliary processes preserve the norm of $x(t)$:

Lemma 3.3: $\|\zeta(t)\| = E[\|x(t)\|]$ for every $t \geq 0$.

Proof: Notice that, if $x \in \mathbb{R}^n$ is nonnegative, then $\|x\| = \mathbb{1}_n^\top x$. Therefore, since $\zeta(t) \geq 0$ and $x(t) \geq 0$, we have $\|\zeta(t)\| = \mathbb{1}_n^\top E[\zeta(t)] = E[(\mathbb{1}_n \eta(t))(\mathbb{1}_n x(t))] = E[\mathbb{1}_n x(t)] = E[\|x(t)\|]$. ■

The following lemma plays an important role in the proof of the main result:

Lemma 3.4: For all $i \in \{1, \dots, n\}$, $h \in [0, T]$, and $t \geq T$, we have $E[\eta_i(t)x(t-h)] = ((u_i^\top e^{\Pi^\top h}) \otimes I_n) \zeta(t-h)$.

Proof: Equation (3) shows that

$$\begin{aligned} E[\eta_i(t)x(t-h)] &= E[E[\eta_i(t)x(t-h) \mid \eta(t-h)]] \\ &= E[E[\eta_i(t) \mid \eta(t-h)]x(t-h)]. \end{aligned} \quad (6)$$

Since $\eta_i = u_i^\top \eta$, we can show $E[\eta_i(t) \mid \eta(t-h)] = E[u_i^\top \eta(t) \mid \eta(t-h)] = u_i^\top e^{\Pi^\top h} \eta(t-h)$. This equation and (6) completes the proof. ■

The next corollary easily follows from Lemma 3.4.

Corollary 3.5: Let $i, j \in \{1, \dots, n\}$ and $t \geq T$ be arbitrary. Define $f_{ij} = p_i^j ((U_{ji} e^{\Pi^\top d_i^j}) \otimes u_j^\top)$ and $g_{ij}(t) = q_i^j(t) ((U_{ji} e^{\Pi^\top t}) \otimes u_j^\top)$. Then, for all i and t , we have

$$\begin{aligned} E[\eta_i(t)(\mathcal{P}_i x)(t)] &= \sum_{j=1}^n f_{ij} \zeta(t - d_i^j), \\ E[\eta_i(t)(Q_i * x)(t)] &= \sum_{j=1}^n (g_{ij} * \zeta)(t). \end{aligned} \quad (7)$$

Proof: From the definition of the operator \mathcal{P}_i , we can show that $\eta_i(t)(\mathcal{P}_i x)(t) = \sum_{j=1}^n u_j \eta_i(t) p_i^j x_j(t - d_i^j) = \sum_{j=1}^n p_i^j u_j u_j^\top \eta_i(t) x(t - d_i^j)$. Taking the expectations in the both hand sides of this equation, from Lemma 3.4 we obtain

$$\begin{aligned} E[\eta_i(t)(\mathcal{P}_i x)(t)] &= \sum_{j=1}^n p_i^j u_j u_j^\top \left((u_i^\top e^{\Pi^\top d_i^j}) \otimes I_n \right) \zeta(t - d_i^j) \\ &= \sum_{j=1}^n p_i^j \left((u_j u_j^\top e^{\Pi^\top d_i^j}) \otimes u_j^\top \right) \zeta(t - d_i^j), \end{aligned}$$

where we used $u_j u_j^\top = u_j \otimes u_j^\top$ and (1) to derive the last equation. This equation proves (7). We can prove the other equation in the same way and hence omit its proof. ■

Using Corollary 3.5, we can then derive the dynamics of the variable ζ as follows:

Proposition 3.6: Define $\bar{A}_0 = \Pi^\top \otimes I_n + \bigoplus_{i=1}^n A_i$, $\bar{A}_{ij} = u_i \otimes f_{ij}$, and $\bar{B}_{ij}(t) = u_i \otimes g_{ij}(t)$, for all $i, j \in \{1, \dots, n\}$ and $t \geq T$. Then, for every $t \geq T$, we have

$$\frac{d\zeta}{dt} = \bar{A}_0 \zeta(t) + \sum_{i,j=1}^n \bar{A}_{ij} \zeta(t - d_i^j) + \sum_{i,j=1}^n (\bar{B}_{ij} * \zeta)(t). \quad (8)$$

Proof: We first derive a differential equation for the extended state variable

$$y = \begin{bmatrix} x \\ \eta \end{bmatrix}.$$

For each $i \in \{1, \dots, n\}$, define the operator \mathcal{A}_i by $(\mathcal{A}_i x)(t) = A_i x(t) + (\mathcal{P}_i x)(t) + (Q_i * x)(t)$. Then, Σ_1 admits the representation $dx/dt = \mathcal{A}_{\varepsilon(t)} x$. Therefore, from the definition of the variables η_i , we can write Σ_1 as

$$\Sigma_1 : \frac{dx}{dt} = \sum_{i=1}^n \eta_i (\mathcal{A}_i x)(t). \quad (9)$$

Also, we know that η follows the stochastic differential equation [20] $d\eta = \sum_{i=1}^n \sum_{j \neq i} (U_{ji} - U_{ii}) \eta dN_{ij}$, where N_{ij} denotes the Poisson counter of rate π_{ij} for each distinct pair $(i, j) \in \{1, \dots, N\}^2$. This equation and (9) show that

$$dy = \begin{bmatrix} \sum_{i=1}^n \eta_i (\mathcal{A}_i x) \\ 0 \end{bmatrix} dt + \sum_{i=1}^n \sum_{j \neq i} \begin{bmatrix} 0 \\ (U_{ji} - U_{ii}) \eta \end{bmatrix} dN_{ij}.$$

Now, applying Lemma 1.2 to the function $\psi(y) = \eta \otimes x = z$, we obtain

$$\begin{aligned} dz &= \frac{\partial z}{\partial y} \begin{bmatrix} \sum_{i=1}^n \eta_i (\mathcal{A}_i x) \\ 0 \end{bmatrix} dt + \\ &\quad \sum_{i=1}^n \sum_{j \neq i} \left[\psi \left(y + \begin{bmatrix} 0 \\ (U_{ji} - U_{ii}) \eta \end{bmatrix} \right) - \psi(y) \right] dN_{ij} \\ &= \sum_{i=1}^n (\eta \otimes I_n) \eta_i (\mathcal{A}_i x) dt + \\ &\quad \sum_{i=1}^n \sum_{j \neq i} [((U_{ji} - U_{ii}) \eta) \otimes x] dN_{ij}, \end{aligned}$$

where we used the identity $\partial \psi / \partial y = [\eta \otimes I_n \ I_n \otimes x]$ in the last equation. Therefore, the expectation ζ obeys the differential equation

$$\begin{aligned} \frac{d\zeta}{dt} &= \sum_{i=1}^n E[(\eta \otimes I_n) \eta_i (\mathcal{A}_i x)] + \\ &\quad \sum_{i=1}^n \sum_{j \neq i} E[[(U_{ji} - U_{ii}) \eta] \otimes x] \pi_{ij}. \end{aligned} \quad (10)$$

Let us compute the expectations in the right hand side of this equation. Since $\eta_i \eta_j = 0$ for $i \neq j$ and $\eta_i^2 = \eta_i$, we have $\eta \eta_i = \eta_i u_i$. Therefore, it follows that $(\eta \otimes I_n) \eta_i (\mathcal{A}_i x) = (u_i \otimes A_i) \eta_i x + (u_i \otimes I_n) \eta_i (\mathcal{P}_i x) + (u_i \otimes I_n) \eta_i (Q_i * x)$. Hence, we can

compute the first term in the right hand side of (10) as

$$\begin{aligned} &\sum_{i=1}^n E[(\eta \otimes I_n) \eta_i (\mathcal{A}_i x)] \\ &= \left(\bigoplus_{i=1}^n A_i \right) \zeta + \sum_{i=1}^n (u_i \otimes I) E[\eta_i (\mathcal{P}_i x)] + \\ &\quad \sum_{i=1}^n (u_i \otimes I_n) E[\eta_i (Q_i * x)] \\ &= \left(\bigoplus_{i=1}^n A_i \right) \zeta + \sum_{i,j=1}^n \bar{A}_{ij} \zeta(t - d_i^j) + \sum_{i,j=1}^n (\bar{B}_{ij} * \zeta)(t), \end{aligned}$$

where we used Corollary 3.5 for deriving the last identity. On the other hand, it is shown in the proof of [14, Proposition 5.3] that the second term of the right hand side of (10) equals $(\Pi^\top \otimes I_n) \zeta$. This completes the proof. ■

We are now ready to prove Theorem 3.1:

Proof of Theorem 3.1: Let ϕ and $\varepsilon(0)$ be arbitrary. We first consider the special case of $\lambda = 0$. Assume that the matrix $\bar{T}^{(0)}$ is Hurwitz stable. Then, by Proposition 1.1, the delayed positive linear system (8) is exponentially stable. Notice that the equation (8) is defined only for $t \geq T$. By the stability of the system (8), there exist $C_1 > 0$ and $\rho > 0$ such that

$$\|\zeta(t)\| \leq C_1 e^{-\rho(t-T)} \|\zeta|_{[0,T]}\|. \quad (11)$$

On the other hand, due to the linearity of the system Σ_1 , there exists $C_2 > 0$ such that $\|x|_{[0,T]}\| \leq C_2 \|\phi\|$. Using this inequality, (11), and Lemma 3.3, we can show that $E[\|x(t)\|] \leq C_1 C_2 e^{-\rho(t-T)} \|\phi\|$. This shows the exponential stability of Σ_1 .

For the general case, observe that the variable $\tilde{x}(t) = e^{-\lambda t} x(t)$ satisfies the stochastic differential equation

$$\tilde{\Sigma}_1 : \frac{d\tilde{x}}{dt} = (A_{\varepsilon(t)} - \lambda I) \tilde{x}(t) + (\mathcal{P}_{\varepsilon(t)}^{(\lambda)} \tilde{x})(t) + (Q_{\varepsilon(t)}^{(\lambda)} * \tilde{x})(t),$$

where

$$(\mathcal{P}_i^{(\lambda)} \tilde{x})(t) = \begin{bmatrix} p_i^1 e^{-\lambda d_i^1} \tilde{x}(t - d_i^1) \\ \vdots \\ p_i^n e^{-\lambda d_i^n} \tilde{x}(t - d_i^n) \end{bmatrix}, \quad Q_i^{(\lambda)}(t) = e^{-\lambda t} Q_i(t),$$

for all $i \in \{1, \dots, n\}$ and $t \geq 0$. Applying the above argument on exponential stability to $\tilde{\Sigma}_1$, we can show that $\tilde{\Sigma}_1$ is exponentially stable if $\bar{T}^{(\lambda)}$ is Hurwitz stable. This completes the proof of the theorem because $\tilde{\Sigma}_1$ is exponentially stable if and only if the growth rate of Σ_1 is less than λ . ■

IV. GROWTH RATE WITH DELAYED ADAPTATION

In this section, we study the population model Σ_2 given in (5) for the case of delayed adaptation. We show that we can characterize the growth rate of the populations as the maximum real eigenvalue of a Metzler matrix, under the assumption that the delays are described by a class of distributions called Coxian distributions. We focus on the case $n = 2$ for simplicity of presentations.

We consider the situation where the population as a whole updates its knowledge σ about the environment in the following stochastic manner:

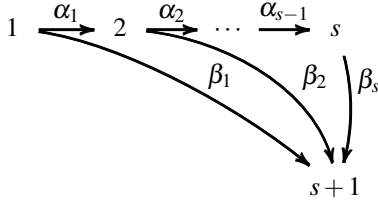


Fig. 1. State transition diagram of the Coxian distribution describing the response delay T_{12} . 1 is the entering state and $s+1$ is the absorbing state.

- 1) When the environment changes from i to j at a time t_0 such that $\sigma(t_0) = i$, a random number T_{ij} is independently drawn from a distribution X_{ij} .
- 2) If the environment ε remains to be j until the time $t_0 + T_{ij}$, then $\sigma(t)$ becomes j at time $t_0 + T_{ij}$.
- 3) If the value of ε changes before the time $t_0 + T_{ij}$, then we discard the number T_{ij} and go back to the first step.

In other words, if we let $t_1 > t_0$ denote the next (minimum) time at which ε changes, then we have

$$\sigma(t) = \begin{cases} \sigma(t_0), & t_0 \leq t \leq \min(t_0 + T_{ij}, t_1), \\ \varepsilon(t_0^+), & \min(t_0 + T_{ij}, t_1) \leq t < t_1. \end{cases}$$

We call the distributions X_{ij} , or, the random times T_{ij} as the response delays.

We allow the response delays to follow a general class of distributions called Coxian distributions defined as follows. For $\alpha \in \mathbb{R}_+^{s-1}$ and $\beta \in \mathbb{R}_+^s$, consider the time-homogeneous Markov process having the state transition diagram in Fig. 1. We say that a random variable follows the Coxian distribution (see, e.g., [22]), denoted by $C(\alpha, \beta)$, if it is the absorption time of the Markov process into state $s+1$ starting from state 1. It is known that the set of Coxian distributions is dense in the set of positive valued distributions [21]. Moreover, there are efficient fitting algorithms to approximate a given arbitrary distribution by a Coxian distribution [22]. We can now formally state our assumptions on the response delays:

Assumption 4.1: There exist $\alpha, \gamma \in \mathbb{R}_+^{s-1}$ and $\beta, \delta \in \mathbb{R}_+^s$ such that T_{12} and T_{21} follow the Coxian distributions $C(\alpha, \beta)$ and $C(\gamma, \delta)$, respectively.

Combining the Markovian dynamics of the environment ε as well as the state transition diagrams for the response delays $T_{12} = C(\alpha, \beta)$ and $T_{21} = C(\gamma, \delta)$, we can easily prove the following proposition.

Proposition 4.2: Consider the time-homogeneous Markov process θ having the state space

$$S = \{(1, 1_0), (2, 1_1), \dots, (2, 1_s), (2, 2_0), (1, 2_1), \dots, (1, 2_s)\}$$

and the state transition diagram in Fig. 2. Assume that $\theta(0) = (\varepsilon(0), \varepsilon(0)_0)$. Define the function $f: S \rightarrow \{1, 2\} \times \{1, 2\}$ by $f(i, j_k) = (i, j)$ for all $i, j \in \{1, 2\}$ and $k \in \{0, \dots, s\}$. Then, $f(\theta) = (\varepsilon, \sigma)$.

From Proposition 4.2, we can represent the population dynamics Σ_2 as $dx/dt = A_{f(\theta(t))}x(t)$, where, for each $i, j \in \{1, 2\}$, the matrix $A_{(i,j)}$ is defined by

$$A_{(i,j)} = \begin{bmatrix} g_i^1 - \omega_j^{12} & \omega_j^{21} \\ \omega_j^{12} & g_i^2 - \omega_j^{21} \end{bmatrix}. \quad (12)$$

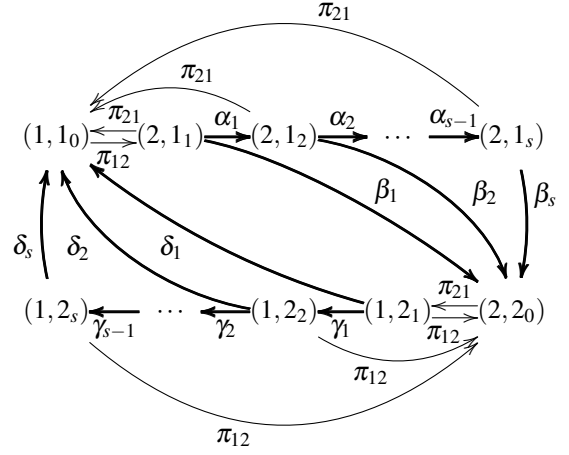


Fig. 2. Markov chain for the dynamics of the pair (ε, σ) . The thick arrows represent the dynamics of phase-type distributions, while the thin arrows represent changes in the environment.

We now present the second main result of this paper, which gives the growth rate of Σ_2 :

Theorem 4.3: Define $\Xi \in \mathbb{R}^{(2s+2) \times (2s+2)}$ by

$$\Xi = \begin{bmatrix} -\pi_{12} & \pi_{12}u_1^\top & 0 & O_{1,s} \\ \pi_{21}\mathbb{1}_s & \Xi_\alpha - \pi_{21}I_s - \text{diag}(\beta) & \beta & O_{s,s} \\ O_{s,1} & O_{s,s} & -\pi_{21} & \pi_{21}u_1^\top \\ \delta & O_{1,s} & \pi_{12}\mathbb{1}_s & \Xi_\gamma - \text{diag}(\delta) - \pi_{12}I_s \end{bmatrix},$$

where

$$\Xi_\alpha = \begin{bmatrix} O_{s-1,1} & \text{diag}(\alpha) \\ 0 & O_{1,s-1} \end{bmatrix} - \begin{bmatrix} \text{diag}(\alpha) & O_{s-1,1} \\ O_{1,s-1} & 0 \end{bmatrix}$$

and Ξ_γ is defined in the same manner. Then, the growth rate of Σ_2 equals the maximum real eigenvalue of the matrix

$$\Xi^\top \otimes I_2 + \bigoplus (\bar{A}_{(1,1)}, I_s \otimes \bar{A}_{(2,1)}, \bar{A}_{(2,2)}, I_s \otimes \bar{A}_{(1,1)}). \quad (13)$$

Proof: It is easy to see that Ξ defined in the theorem gives the infinitesimal generator of the Markov process θ . Therefore, by [14, Theorem 5.2], the growth rate of Σ_2 equals the maximum real eigenvalue of the Metzler matrix

$$\Xi^\top \otimes I_2 + \bigoplus (A_{f(1,1_0)}, A_{f(2,1_1)}, \dots, A_{f(2,1_s)}, A_{f(2,2_0)}, A_{f(1,2_1)}, \dots, A_{f(1,2_s)}).$$

The direct sum in this matrix equals the second term of (13) since $A_{f(2,1_k)} = A_{(2,1)}$ and $A_{f(1,2_k)} = A_{(1,2)}$ for all k by the definition of the matrices $A_{(i,j)}$ in (12). This completes the proof of the theorem. \blacksquare

V. NUMERICAL SIMULATIONS

In this section, we present numerical simulations to illustrate the results obtained in the previous sections. For simplicity of presentation, we focus on the case $n = 2$; i.e., there are only two phenotypes in the population under consideration. We use the parameters $g_1^1 = 1$, $g_1^2 = 0.05$, $g_2^1 = -2$, and $g_2^2 = 0.95$. These parameters indicate that the phenotypes 1 and 2 are fitted to the environment 1 and 2, respectively. We set the phenotypic transition rates as $\omega_1^{12} = \omega_2^{21} = 0.1$ and $\omega_1^{21} = \omega_2^{12} = 1$.

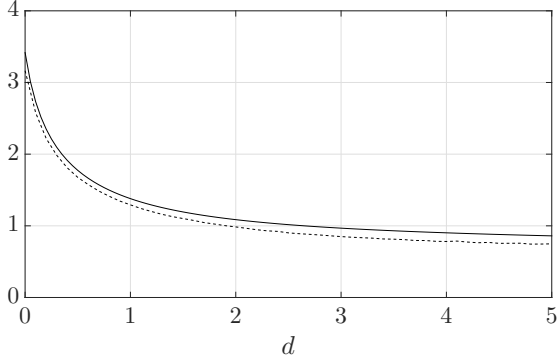


Fig. 3. Growth rates of Σ_1 . Solid: Upper bounds (Theorem 3.1). Dashed: Sample averages of $T^{-1} \log(\|x(T)\|/\|\phi\|)$ with $T = 50$.

First, we illustrate Theorem 3.1 for the case of delayed proliferation. We consider only point delays; therefore, it is assumed that $q_i^k(t) \equiv 0$ for all $i, k \in \{1, 2\}$. Furthermore, we assume that both the delays and the rate of delayed proliferation are homogeneous, that is, there exist $d \geq 0$ and $p \geq 0$ such that $d_i^k = d$ and $p_i^k = p$ for every $i, k \in \{1, 2\}$. We set the initial state as $\phi(t) = [1 \ 1]^\top$ for every $t \in [-d, 0]$. Using Theorem 3.1 and bisection search, we compute the suboptimal upper bounds on the growth rates of Σ_1 for $p = 2.5$ and $d \in [0, 5]$. To examine the accuracy of the upper bounds, we numerically compute the quantity $50^{-1} \log(E[\|x(50)\|]/\|\phi\|)$ using 500 sample paths for each pair of (d, p) . The above two quantities are shown in Fig 3. Their relative differences are less than 10%, showing the accuracy of the upper bounds by Theorem 3.1. We have also confirmed that, as $d \rightarrow \infty$ or $p \rightarrow 0$, the upper bounds approach to the common value 0.6863, which equals the growth rate of the population model Σ_0 without delays.

We then focus on delayed adaptation studied in Section IV. Assume that delays X_{12} and X_{21} both follow the Erlang distribution with shape k and mean μ . This distribution is the k -sum of independent exponential distributions with mean μ/k and, therefore, approximates the normal distribution with mean μ and the variance μ^2/k when k is large. From this fact, we can also see that the Erlang distribution is a Coxian distribution having the parameters $s = k$, $\alpha_1 = \dots = \alpha_{k-1} = \beta_k = \lambda = k/\mu$, and $\beta_1 = \dots = \beta_{k-1} = 0$. Using Theorem 4.3, we compute the growth rate of Σ_2 when μ varies over the interval $[0, 10]$. We have used $k = 100$ in this simulation. We show the obtained growth rates in Fig. 4. We have confirmed the following limit phenomena. First, as μ tends to zero, the growth rate approaches to that of the population model Σ_0 without delay. Second, as μ tends to ∞ , the growth rate approaches to that of the population model without adaptation, as expected.

VI. CONCLUSION

In this paper, we have studied the growth rate of bet-hedging populations experiencing delays and environmental changes. By modeling the population dynamics using positive Markov jump linear systems with delays, we have shown

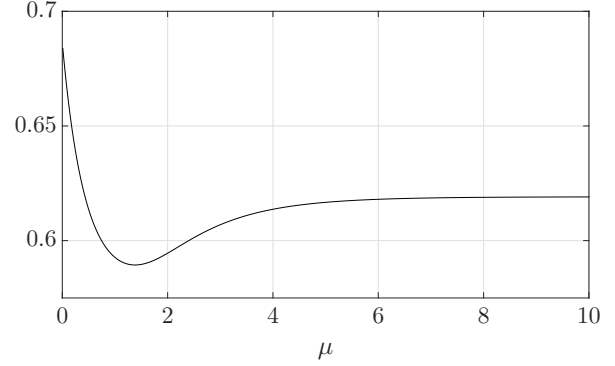


Fig. 4. Growth rate of Σ_2 versus μ

that the growth rates can be upper-bounded by the maximum real eigenvalue of Metzler matrices. In particular, in the case of adaptation delays, the upper bounds give the exact value of the growth rates. We have confirmed the effectiveness of the proposed methods via numerical simulations.

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